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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/078,927
Filing Date: February 19, 2002
Appellant(s): CURRAN ET AL.

Shawn A. Hawkins
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/25/2009 appealing from the Office action mailed 9/3/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect by inconsistently stating, "There are a total of 40 claims in this application", thus suggesting that 40 claims are on appeal, yet further stating, "Claims 1-3, 9, 12, 16-35, and 39-40 have been canceled". A correct statement of the status of the claims is as follows:

This appeal involves claims 4-8, 10-11, 13-15, and 36-38.

Claims 1-3, 9, 12, 16-35, and 39-40 have been canceled.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,323,117 CURRAN et al. 11-2001

KESHVARA et al., "Identification of Reelin-induced Sites of Tyrosyl Phosphorylation on Disabled 1", *J. Biol. Chem.* 276:16008-16014, 2001

NIETHAMMER et al., "NUDEL is a Novel Cdk5 Substrate that Associates with LIS1 and Cytoplasmic Dynein" *Neuron* 28:697-711, 2000

CARR et al., "Selective Detection and Sequencing of Phosphopeptides at the Femtomole Level by Mass Spectrometry", *Analytical Biochem.* 239:180-192, 1996

GenBank GI:1771281, "*M. musculus* mRNA for mDab555 protein", February 1997

GenBank GI 3288851, "*Homo sapiens* disabled-1 (DAB1) mRNA", November 1998

HOWELL et al., "Reelin-induced tyrosine phosphorylation of Disabled 1 during neuronal positioning", *Genes Develop.* 13:643-648, 1999

FU et al., "Cdk5 is involved in neuregulin-induced AChR expression at the neuromuscular junction", *Nature Neurosci.* 4:374-381, 2001

MICHALEWSKI et al., "Immunoblotting with Antiphosphoamino Acid Antibodies: Importance of the Blocking Solution", *Analytical Biochem.* 276:254-257, 1999

ZHEN et al., "Prenatal Exposure to Cocaine Disrupts D1A Dopamine Receptor Function Via Selective Inhibition of Protein Phosphatase 1 Pathway in Rabbit Frontal Cortex", *J. Neurosci.* 21:9160-9167, 2001

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(A) Claim(s) 4-8 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran et al. (US Patent 6,323,177; reference A of the PTO-892 mailed on 1/25/08; hereafter "Curran") in view of Keshvara et al. (*J. Biol. Chem.* 276:16008-16014, 2001; reference AG2 of the IDS filed on 3/25/02; hereafter "Keshvara"), Niethammer et al. (*Neuron* 28:697-711, 2000; reference AM1 of the IDS filed on 3/25/02; hereafter "Niethammer"), Carr et al. (*Analytical Biochem.* 239:180-192, 1996; reference U of the PTO-892 mailed on 6/19/08; hereafter "Carr"), GenBank Accession Number GI:1771281 (February 1997; cited in the PTO-892 mailed on 1/25/08; hereafter "GI:1771281"), and GenBank Accession Number GI:3288851 (November 1998; cited in the PTO-892 mailed on 1/25/08; hereafter "GI:3288851").

CLAIM INTERPRETATION: The method of claims 4-8 and 36-37 requires a single active step of "determining whether the carboxy terminal domain of Disabled 1 protein…in said sample is phosphorylated on a serine within a candidate sequence". The preamble's recitation of "for detecting cyclin dependent kinase 5…serine kinase activity" in claim 36 is interpreted in accordance with MPEP 2111.02 as reciting an

intended use of the claimed method. The wherein clause "wherein phosphorylation of Dab1 on said serine indicates the presence of active Cdk5" in claim 36 is interpreted in accordance with MPEP 2106.II.C as reciting a correlation between Dab1 phosphorylation and Cdk5 activity without limiting the single active step of the claim.

The reference of Curran teaches “In vitro cdk5 can also phosphorylate Dab1 on serine residues” (column 4, lines 46-47) and “In particular, identification of the site of Dab1 phosphorylation may permit its use as a potential target for agonists and antagonists. Cdk5 phosphorylates Dab1 in vitro. We can screen for inhibitors and agonists of this activity in connection with Reelin binding to VLDLR, and map the phosphorylation sites. Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. Thus, this area of exploration has significant relevance” (column 23, line 63 to column 24, line 4).

The differences between Curran and the claimed methods are: Curran does not teach those residues of Dab1 that are phosphorylated by Cdk5; Curran does not teach Dab1 is phosphorylated in biological sample, *e.g.,* brain and blood, from a mouse or human; and Curran does not teach methods of measuring Cdk5 activity by determining whether or not Dab1 is phosphorylated at these residues.

The references of Niethammer, Keshvara, and Carr are cited as showing various methods for analyses of a phosphoprotein. Regarding the limitations of claims 4-5, 7-8, and 36-37, the reference of Niethammer teaches a method for determining the sites of phosphorylation of a substrate polypeptide of Cdk5. For example, the method involves immunoprecipitation of the substrate polypeptide from mouse brain extracts with or

without catalytically active Cdk5 activity and determining whether or not the substrate protein has altered electrophoretic mobility (p. 704, Figures 7A, 7D, and 7E and p. 709, column 1); teaches identifying those amino acids that are potentially phosphorylated by Cdk5 kinase in the primary sequence of the polypeptide, which have serine-proline (p. 703, column 2, bottom and p. 698, Figure 1A); individually and combinatorially mutating the potential Cdk5-phosphorylated serine residue to an alanine; comparing the electrophoretic mobility shift in migration of immunoprecipitated wild-type and mutant proteins in the presence and absence of catalytically active Cdk5 in COS7 cells; and identifying those residues that are phosphorylated by Cdk5 by comparing the Cdk5 phosphorylation of the wild-type, individual mutants, and combinatorial mutants (p. 704, Figure 7F and p. 708, column 1 to p. 709, column 2).

Regarding the limitations of claims 6-7 and 36-37, the reference of Keshvara teaches a method of identifying sites of tyrosine phosphorylation of Dab1 by Src, using a method similar to that of Niethammer, wherein the tyrosine residues phosphorylated by Src are identified by mutating each potential Src-phosphorylated tyrosine to phenylalanine and analyzed by autoradiography and tryptic phosphopeptide analysis (p. 16009, Figure 1A-B and column 1 under *Kinase Reactions* and *Phosphopeptide Mapping;* p. 16010, Figure 2A-B). Keshvara teaches an expression vector encoding Dab1 for use in expressing Dab1 in a eukaryotic cell (p. 16009, under *Cell Culture and Immunoprecipitations*).

Regarding the limitations of claims 36-37, the reference of Carr teaches a method for detecting and sequencing phosphopeptides from an enzymatic digest of a phosphoprotein by mass spectrometry (p. 180, abstract).

Regarding the limitations of claims 36-37, GenBank Accession Numbers 1771281 and 3288851 disclose the amino acid sequences of murine Dab1 and human Dab1, respectively. Given these sequences at the time of the invention, a skilled artisan would have recognized that by visually inspecting the amino acid sequences of murine and human Dab1 as shown by GenBank Accession Numbers 1771281 and 3288851, respectively, five potential Cdk5 serine-proline phosphorylation sites (as disclosed by Niethammer as noted above) are present at positions 260, 400, 481, 491, and 515.

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from a mouse brain extract with and without catalytically active Cdk5 (as taught by Niethammer) and analyze its electrophoretic mobility and to determine whether or not serine at positions 260, 400, 481, 491, and 515 are phosphorylated in accordance with the methodology of Niethammer and Keshvara. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates Dab1; the sites of Cdk5 phosphorylation of Dab1 can be identified; and may have “significant relevance” to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. One would have had a reasonable expectation of success

to immunoprecipitate Dab1 from a mouse brain extract with and without catalytically active Cdk5 (as taught by Niethammer) and analyze its electrophoretic mobility and to determine whether or not serine at positions 260, 400, 481, 491, and 515 are phosphorylated in accordance with the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the phosphopeptide analysis method of Carr. By doing this, one of ordinary skill in the art would have practiced the active method step(s) as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates Dab1; the sites of Cdk5 phosphorylation of Dab1 can be identified; and may have "significant relevance" to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. One of ordinary skill in the art would have had a reasonable expectation at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the phosphopeptide analysis method of Carr. Therefore, the method of claims 4-8 and 36-37 would have been obvious to one of ordinary skill in the art at the time of the invention.

(B) Claim(s) 10-11, 13-15, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran in view of Keshvara, Niethammer, Carr, and GenBank Accession Numbers 1771281 and 3288851 as applied to claims 4-8 and 36-37 above and further in view of Howell et al. (*Genes Develop.* 13:633-648, 1999; reference AY1 in the IDS filed on 3/25/02; hereafter "Howell"), Fu et al. (*Nature Neurosci.* 4:374-381; reference X of the PTO-892 mailed on 1/25/08 ; hereafter "Fu"), Michalewski et al. (*Analytical Biochem.* 276:254-257, 1999; reference U of the PTO-892 mailed on 1/25/08; hereafter "Michalewski"), and Zhen et al. (*J. Neurosci.* 21:9160-9167, 2001; reference V of the PTO-892 mailed on 1/25/08; hereafter "Zhen").

CLAIM INTERPRETATION: The method of claims 10-11, 13-15, and 38 requires three active steps as follows: 1) immunoprecipitation of Dab1 from said biological sample; 2) contacting the immunoprecipitated Dab1 with a phosphoantibody generated using SEQ ID NO:3 as an antigen; and 3) detecting binding of the phosphoantibody to a serine within a candidate sequence in the carboxy terminal domain of Dab1. The preamble's recitation of "for detecting cyclin dependent kinase 5…serine kinase activity" in claim 38 is interpreted in accordance with MPEP 2111.02 as reciting an intended use of the claimed method. The wherein clause "wherein binding of the phosphoantibody to said serine of said Dab1 in such biological sample indicates the presence Cdk5 serine kinase activity in said sample" in claim 38 is interpreted in accordance with MPEP 2106.II.C as reciting a correlation between Dab1 phosphorylation and Cdk5 activity without limiting the three active steps of the claim.

The relevant teachings of Curran, Niethammer, Keshvara, Carr, and GenBank Accession Numbers 1771281 and 3288851 as applied to claims 4-8 and 36-37 are set forth above. The combination of references does not appear to teach or suggest using a antiphosphoserine antibody, optionally raised against SEQ ID NO:3, to detect sites of Cdk5 phosphorylation.

However, with respect to the limitations of claims 10, 15, and 38, at the time of the invention methods for analyzing protein phosphorylation using antiphosphoamino acid antibodies were well-known in the prior art. Precedent for using an antiphosphoamino acid antibody for identifying Cdk5 phosphorylated serines is provided by the reference of Fu, which teaches a method for analyzing Cdk5 serine phosphorylation of ErbB3 using a commercially available anti-phosphoserine antibody (p. 377, Figure 5; p. 379 under "*Chemicals and antibodies*; and p. 380 under *In vitro phosphorylation assay*). Precedent for using an antiphosphoamino acid antibody for analyzing Dab1 phosphorylation is provided by the reference of Howell, which teaches a method for analyzing *in vivo* and *in vitro* Dab1 tyrosine phosphorylation using an anti-tyrosine antibody (p. 645, Figures 2-3 and p. 646, Figure 4).

Regarding the limitation of claim 13, the reference Michalewski teaches a polyclonal antiphosphoserine antibody (p. 254, column 2, middle).

Regarding the limitation of claim 14, the reference of Zhen teaches a monoclonal antiphosphoserine antibody (p. 9161, column 2, middle).

Regarding the phosphoantibody recited in claims 11 and 38, the recited phosphoantibody is a product-by-process, being "raised against" SEQ ID NO:3 (claim

11) or "generated using SEQ ID NO:3 as an antigen" (claim 38). According to the sequence listing filed on 1/2/09, SEQ ID NO:3 is a phosphopeptide corresponding to amino acids 484 to 497 of Dab1 with Ser at position 491 being phosphorylated. The examiner has broadly, but reasonably interpreted the phosphoantibody recited in claims 11 and 38 in accordance with MPEP 2113 as encompassing an antiphosphoserine antibody that is capable of binding to the phosphopeptide of SEQ ID NO:3, which includes the antiphosphoserine antibodies of Fu, Michalewski, and Zhen. This interpretation is undisputed by appellant.

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu, Michalewski, and Zhen to analyze the phosphorylation of mouse Dab1 at positions 260, 400, 481, 491, and 515 by using a monoclonal or polyclonal anti-phosphoserine antibody. One would have been motivated to do this because Curran expressly teaches that Cdk5 phosphorylates serines of Dab1 and the sites of Cdk5 phosphorylation of Dab1 can be identified and exploited to screen for agonists and antagonists as described above and the use of an anti-phosphoserine antibody to detect phosphoserine avoids of the use of hazardous radioactivity. One would have had a reasonable expectation of success to analyze the phosphorylation of mouse Dab 1 at positions 260, 400, 481, 491, and 515 by using an anti-phosphoserine antibody because of the results of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu,

Michalewski, and Zhen. Therefore, the method of claims 10-11, 13-15, and 38 would have been obvious to one of ordinary skill in the art at the time of the invention.

(10) Response to Argument

(A) Beginning at p. 3 of the Appeal Brief filed on 11/25/09 (hereafter "the Brief"), appellant argues the purpose of the claimed methods is a nonobvious, limiting element of the claimed invention. According to appellant, the invention is based on the discovery that Dab1 is selectively phosphorylated by Cdk5 on Ser491 and Ser515. Appellant argues this discovery is important and non-obvious because it provides a method for detecting Cdk5 activity in a biological sample, which method is different from a method for determining the sites of Dab1 phosphorylation by Cdk5. According to appellant, there was no way to predict *a priori* that certain sites in Dab1 would be phosphorylated only by Cdk5 and provide a method for detecting Cdk5 activity and none of the prior art references teaches or suggests that Dab1 is selectively serine phosphorylated by Cdk5.

Appellant's argument is not found persuasive. The examiner maintains the position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention. While the prior art clearly teaches or suggests Dab1 phosphorylation by Cdk5, the examiner acknowledges that the combination of references does not appear to explicitly teach or suggest phosphorylation of Dab1 by Cdk5 *only at residues Ser491 and Ser515.* However, the examiner maintains the position that by practicing the method as taught or suggested by the combination of prior art (as noted previously at pp. 7-8 of the Office action mailed on 6/19/08), one would have *necessarily* practiced a method that is encompassed by the claims. In other

words, because Cdk5 selectively phosphorylates Dab1 only at serine residues 491 and 515, by practicing the method as taught or suggested by the prior art, one would have necessarily determined whether the “carboxyl end” of Dab1 or serine positions 491 (corresponding to position 3 of SEQ ID NO:1) and 515 (corresponding to position 21 of SEQ ID NO:2) are phosphorylated.

Although appellant takes the position that a method for detecting Cdk5 serine kinase activity in a biological sample is different from the method as taught or suggested by the prior art, appellant fails to point out with particularity the difference(s) between the claimed method and the method as taught or suggested by the prior art. Put another way, there is no objective evidence or line of reasoning to support the position that the method as taught or suggested by the prior art is not encompassed by the method as claimed. While the examiner acknowledges the preamble’s recitation of “method for detecting cyclin dependent kinase 5…serine kinase activity in a biological sample", this recitation has been interpreted as an intended use of the claimed method and has been accorded no patentable weight with respect to the active method steps of the claims. See MPEP 2106.II.C, which states, “Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation”. To the extent the recitation of “in a biological sample” may limit the claimed method, this limitation is satisfied by the prior art teachings set forth above, which disclose detecting phosphorylation of a substrate polypeptide in a sample from a cell culture or a mouse.

Beginning at p. 4 of the Brief, appellant traverses this position, asserting the "purpose" of the claimed methods appears in the both the preamble and the body of the claims and further asserts "this [purpose] is a critical feature of the claimed method that is intended to limit its scope". According to appellant, the examiner's position is "weak", asserting MPEP 2106.II.C is directed to a determination of statutory subject matter under 35 U.S.C. 101 and is not directed to an obvious analysis. Appellant argues that the stated purpose is not optional and cannot be ignored and requires the step of associating Dab1 serine phosphorylation with Cdk5 activity. Appellant argues that in this case, the stated preamble is "clearly limiting…and is used to distinguish the claim from the prior art".

Appellant's argument is not found persuasive. As to appellant's remarks regarding the relevance of MPEP 2106.II.C to the instant rejection, it is clear that this section of MPEP is relevant to claim analysis and interpretation and is not to be limited to an analysis of statutory subject matter. Although appellant asserts the preamble's recitation of "for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample" and the recitation of the wherein clause "wherein phosphorylation of Dab1 on said serine indicates the presence of active Cdk5 in said sample" are limiting and distinguish the claimed invention over the prior art, the examiner maintains that these recitations are non-limiting with respect to the active method step(s) and have been accorded no patentable weight. The preamble recites the intended use of the claimed methods and does not limit the active method step(s) of the claims. As noted above, to the extent the recitation of "in a biological sample" may limit the claimed

method, this limitation is satisfied by the prior art teachings set forth above, which disclose detecting phosphorylation of a substrate polypeptide in a sample from a cell culture or a mouse. The "wherein" clause also does not limit the active method step(s) of the claims, instead merely reciting a correlation between Dab1 phosphorylation and the presence of Cdk5.

Beginning at p. 5 of the Brief, appellant argues there is no motivation in the prior art to combine the references "in the manner suggested by the examiner". According to appellant, although Curran acknowledges Dab1 phosphorylation by Cdk5 *in vitro,* because none of the cited prior art references discloses selective Dab1 phosphorylation by Cdk5 *in vivo,* there is no motivation to inspect murine or human Dab1 sequences for phosphorylation at serine position 491 or 515. According to appellant, only with the knowledge of selective phosphorylation of Dab1 by Cdk5 at serine position 491 or 515, as identified by appellant, would one have been motivated to detect Cdk5 activity by determining whether or not Dab1 is phosphorylated by Cdk5 at serine position 491 or 515.

Appellant's argument is not found persuasive. Contrary to appellant's position, one of ordinary skill in the art need not have known Dab1 is selectively phosphorylated by Cdk5 at serine position 491 or 515 in order to practice the invention *as claimed.* Appellant appears to take the position that the absence of knowledge that Dab1 is selectively phosphorylated by Cdk5 at serine position 491 or 515 would not motivate or even teach away from practicing the claimed invention. However, as noted above, by practicing the methods taught or suggested by the prior art, one would have necessarily

practiced the claimed invention. Moreover, in view of the combination of prior art, one of ordinary skill in the art would have been motivated to identify the sites of Dab1 phosphorylation by Cdk5. For example, Curran suggests the potential biological relevance of Cdk5 phosphorylation of Dab1 *in vivo* and Niethammer teaches the polypeptide NUDEL is an *in vitro* target of Cdk5, which leads Niethammer to determine if NUDEL is an *in vivo* physiological substrate of Cdk5 (p. 703, column 2 to p. 705, column 1). Moreover, one would have selected Dab1 at serine positions 491 and 515 as well as positions 260, 400, and 481 for the presence of a phosphoserine because Niethammer teaches the consensus sequence that is phosphorylated by Cdk5, which serines at this consensus sequence are present at Dab1 positions 260, 400, 481, 491 and 515 in the amino acid sequences of GenBank Accession Numbers 1771281 and 3288851. As such, absence of a disclosure that Dab1 is selectively phosphorylated by Cdk5 at serine position 491 or 515 *in vivo* would not have been taken by one of ordinary skill in the art as a teaching away from practicing the claimed invention. Contrary to appellant's position, absence of such a disclosure would have actually motivated one of ordinary skill in the art to practice the claimed invention as written.

At least for the reasons stated above, the examiner maintains the position that the combination of cited references properly establishes a *prima facie* case of obviousness.

(B) Beginning at p. 7 of the Brief, appellant argues it was not obvious that Cdk5 serine kinase activity could be determined by determining the Dab1 serines that are

phosphorylated by Cdk5 and that none of the cited references suggests Ser491 and Ser515 of Dab1 as being phosphorylated only by Cdk5. Thus, according to appellant, because there is nothing in the prior art references of Curran, Keshvara, Niethammer, Carr, and GenBank Accession Numbers 1771281 and 3288851 to teach and/or suggest the methods of claims 4-8 and 36-37, one would not have further combined Howell, Fu, Michalewski and Zhen and the methods of claims 10-11, 13-14 and 38 would not have been obvious at the time of the invention.

Appellant's argument is not found persuasive. The examiner maintains the position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention. The examiner acknowledges that the combination of references does not appear to explicitly teach or suggest phosphorylation of Dab1 by Cdk5 *at residues Ser491 and Ser515*. However, at least for the reasons set forth above, the examiner maintains the position that by practicing the method as taught or suggested by the combination of references, one would have necessarily practiced the method step(s) that is/are encompassed by the claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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